# METHOD FOR TARGETED THERAPEUTIC DELIVERY OF PROTEINS INTO CELLS

## SUMMARY

The Protein Expression Laboratory at the National Cancer Institute in Frederick, MD is seeking statements of capability or interest from parties interested in collaborative research to further develop a platform technology for the targeted intra-cellular delivery of proteins using virus-like particles (VLPs).

## REFERENCE NUMBER

E-010-2008

## PRODUCT TYPE

- Devices
- Therapeutics
- Vaccines

## KEYWORDS

- Virus-like particles
- VLP

## COLLABORATION OPPORTUNITY

This invention is available for licensing.

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## DESCRIPTION OF TECHNOLOGY

Current methods to deliver proteins into cells (e.g., using retrovirus, DNA transfection, protein transduction, microinjection, complexing the protein with lipids, etc.) have many shortcomings, such as lack of target specificity toxicity, or unwanted random integration into the host chromosome. Protein transduction is an emerging technology for delivering proteins into cells by exploiting the ability of certain proteins to penetrate the cell membrane. However, the majority of the proteins delivered by this means are usually trapped and subsequently degraded in the endosomes-lysosomes of recipient cells.

This invention describes a method for the delivery of proteins into cells using virus-like particles (VLPs) either in a non-targeted or a targeted way. VLPs are structures resembling a virus particle capable of self-assembly into nanoparticles, but are non-replicating because they lack viral nucleic acids. The technology is based on fusion of protein(s) of interest with GAG structural protein of Rous Sarcoma Virus (RSV)

pseudotyped with VSV-G (glycoprotein envelope) or its mutant form for targeted delivery. In addition, a chimeric VLP could be used to deliver functional fusion proteins or fully-processed proteins (protease) into the cytoplasm or nucleus of target cells. Since the problem of endosomal entrapment is eliminated, proteins can be delivered to target cells more efficiently than existing protein transduction methods. Contrary to retroviral-mediated gene delivery, no genetic retroviral material is incorporated into VLP. This allows for safe protein delivery and eliminates unsafe incorporation of retroviral DNA into the host chromosome.

The inventors have validated the biological activity of Cre recombinase and cytotoxic enzymes delivered using VLPs in a human prostate cancer cell line. Specific ligands such as TNF-related apoptosis-inducing ligand (TRAIL) can be displayed on the surface of hybrid VLPs. In vitro assays indicated that VLP-mediated TRAIL delivery is at least twice as effective and required 1000 times less peptide than soluble TRAIL, which is currently under clinical trial elsewhere.

In addition to protein therapy that might be used to treat numerous diseases and disorders, this technology can also be used for expansion of stem cells for transplantation as well as for the development of cancer vaccines.

Further R&D Needed:

- In vivo studies on mouse models
- Capability of conducting in vivo studies in larger animals is desired.
- Collaborations regarding any aspect of the VLP-delivery platform technology will be considered

R&D Status: Pre-clinical in-vitro proof of concept with human prostate cancer cell lines indicated VLP-mediated TRAIL delivery is at least twice as effective and requires 1000 times less peptide than soluble TRAIL.

## POTENTIAL COMMERCIAL APPLICATIONS

- Intracellular targeted delivery of therapeutic proteins.
- Ex vivo use for expansion of stem cells for transplantation.
- Antigen loading of dendritic cells for cancer vaccination.

## COMPETITIVE ADVANTAGES

- Platform technology that could be applied to the targeted killing of tumors, protein therapy, stem cell generation, and cancer vaccine development
- Transformations of VLPs permits targeting of specific receptors on cells
- Proteins are not trapped and degraded in the endosomes/lysosomes of target cells.
- Lack of genetic retroviral materials in VLP allows safe protein delivery and eliminates potentially unsafe incorporation of retroviral DNA into host chromosome.

## INVENTOR(S)

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## DEVELOPMENT STAGE

- Pre-clinical (in vivo)

## PATENT STATUS

- **U.S. Filed:** U.S. Patent Application No. 61/195,084 filed 03 Oct 2008 (HHS# E-010-2008/0)

## THERAPEUTIC AREA

- Cancer/Neoplasm